REMARKS

I. Status Summary

Claims 1-17 and 80 are pending in the present U.S. patent application and have been examined.

Claims 1-17 and 80 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specification does not reasonably provide enablement for a method of screening for susceptibility to sub-optimal norepinephrine (NE) transport in a subject.

Claims 1, 4-6, 8, 14, and 15 have been amended. Support for the amendments can be found throughout the specification as filed, including particularly at page 12, lines 17-19 (sub-optimal NE transport resulting in decreased NE clearance). Additional support can be found at 13, lines 11-14 (SEQ ID NO: 15 includes exon 9) and at page 13, lines 20-22 (SEQ ID NO: 1 is a human NET cDNA).

New claim 81 has been added. Support for the new claim can be found throughout the specification as filed, including particularly at page 12, lines 4-9. Additional support can be found at page 13, lines 11-17, in original claims 42 and 55, in Figure 2, and in the Sequence Listing.

No new matter has been added by the amendments to the claims or the addition of the new claims.

Reconsideration of the application based on the remarks sets forth herein below is respectfully requested.

II. Response to the Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-17 remain rejected, and claim 80 is newly rejected, under 35 U.S.C. § 112, first paragraph, upon the contention that the specification, while being enabled for a method of screening for susceptibility to sub-optimal norepinephrine (NE) transport in orthostatic intolerance (OI), does not reasonably provide enablement for a method of screening for susceptibility to sub-optimal NE transport in a subject. According to the United States Patent and Trademark Office (hereinafter "the Patent Office"), the

specification does not enable any person skilled in the art to which it pertains to use the invention commensurate in scope with the claims.

After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection and submit the following remarks.

In support of the instant rejection, the Patent Office asserts that the specification does not demonstrate any correlation between NE transport in general with any specific mutation except for the correlation between the A457P mutation in orthostatic intolerance, thus the specific mutation was correlated with NE transport in orthostatic intolerance (OI) and not with general NE transport in a subject. In response, applicants argued in an Amendment filed March 22, 2005, that the Patent Office had offered no sound scientific basis for asserting that a mutation that results in an amino acid change in the norepinephrine (NE) transporter (NET) gene product that results in sub-optimal NE transport in OI patients would not be expected to result in sub-optimal NE transport in patients not suffering from OI. Applicants asserted that the gene in question is the NE transporter itself. Applicants thus contended that the Patent Office's implicit assertion that transport through an NET polypeptide having an A457P in OI patients would be expected to be different than transport through an NET polypeptide having an A457P in non-OI patients cannot be supported by adequate scientific or technical reasoning as is required under M.P.E.P. Section 2164.04. Accordingly, applicants asserted that the Patent Office's assertion failed to support the instant rejection under 35 U.S.C. § 112, first paragraph.

In an Advisory Action dated April 13, 2005, the Patent Office reiterated its contention that the specification only enables a specific mutation (A457P) in OI patients with sub-optimal NE transport and does not enable any other mutation in NET or mutations in non-OI patients. Applicants respectfully maintain, however, that the Patent Office has not provided any sound, scientific basis for the contention that a mutation in the norepinephrine transporter (NET) that results in sub-optimal norepinephrine transport in one group of patients (*e.g.*, OI patients) would not also result in sub-optimal NE transport in another group of patients (*e.g.*, non-OI patients) as is believed to be required by the case law and the M.P.E.P.

To elaborate, applicants respectfully submit that the Training Materials for Examining Patent Applications with Respect to 35 U.S.C. § 112, First Paragraph – Enablement Chemical/Biotechnical Applications (hereinafter the "Training Materials") clearly states: "to object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the examiner must provide evidence or technical reasoning substantiating those doubts" (*citing* In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) and M.P.E.P. Section 2164.04; emphasis added). Additionally, the Training Materials state: "without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling" (*citing* In re Wright at page 1562 and In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971); emphasis added). The Training Materials thus concludes that "the case law makes clear that properly reasoned and supported statements explaining any failure to comply with Section 112 are a requirement to support a rejection" (*citing* In re Wright at page 1562; emphases added).

Applicants respectfully submit that the gene at issue is the NE transporter itself. Thus, applicants respectfully submit that one of ordinary skill in the art would understand, after a review of the disclosure of the present U.S. patent application, that mutations in NET that result in altered NE transport activity could result in sub-optimal NE transport in a cell autonomous manner that does not depend on the interaction of any additional genetic or non-genetic factors that might be present in the OI or the non-OI subject. As a result, applicants respectfully submit that the Patent Office has not, and indeed cannot, provide the required "properly reasoned and supported statement" that an NET mutation that results in sub-optimal NE transport in OI patients would not also result in sub-optimal NE transport in non-OI patients.

Furthermore, applicants respectfully submit that the Patent Office's assertion that "the generalized statement that a mutation in NET would be predicted to function in OI patients and non-OI patients similarly with respect to NE transport is not persuasive" is an improper attempt to shift the burden of proof to applicants before the Patent Office has successfully established a *prima facie* case of lack of enablement. Applicants

respectfully submit that the Patent Office has the burden of establishing, by properly reasoned and supported statements, that mutations in the NE transporter would be expected to function differently in OI and non-OI patients. Applicants respectfully submit that the Patent Office has not met this burden.

Applicants further respectfully submit that the Patent Office's current contentions in support of the instant rejection fall particularly short of establishing a *prima facie* case of failure to comply with 35 U.S.C. § 112, first paragraph, with respect to claims 5-7. Claim 5 recites a method of screening for susceptibility to sub-optimal norepinephrine (NE) transport resulting in decreased NE clearance in a subject, the method comprising (a) obtaining a biological sample from the subject, wherein the biological sample comprises a nucleic acid sample; and (b) detecting a polymorphism of a NE transporter gene in the biological sample from the subject, wherein the polymorphism of the NE transporter gene comprises a G to C transversion within NE transporter exon 9 (nucleotides 129-257 of SEQ ID NO: 15) and encodes a NE transporter polypeptide having a proline moiety at amino acid 457 of SEQ ID NO: 1, the presence of the polymorphism indicating the susceptibility of the subject to sub-optimal norepinephrine transport. Applicants respectfully submit that this claim recites the A457P mutation that the Patent Office concedes is enabled, and thus there is no basis for this rejection other than the apparent contention that this claim must be limited to OI patients.

As applicants believe that they have addressed the impropriety of this assertion hereinabove, applicants respectfully submit that claim 5 is in condition for allowance. Furthermore, applicants respectfully submit that claims 6 and 7, which depend from claim 5, are also believed to be in condition for allowance based on the remarks presented with respect to claim 5. Accordingly, applicants respectfully request that the rejection of claims 5-7 under 35 U.S.C. § 112, first paragraph, be withdrawn at this time.

In conclusion, applicants respectfully submit that the specification as filed teaches techniques that can be used for identifying nucleic acids encoding polymorphic NET polypeptides present in subjects, and further for assaying the NE transport activities of these polypeptides to identify polymorphisms that are associated with sub-optimal NE transport. Thus, applicants respectfully submit that the specification as filed

teaches one of ordinary skill in the art how to screen subjects for susceptibility to sub-optimal NE transport as recited in the claims without undue experimentation.

Accordingly, applicants respectfully submit that the current rejection of claims 1-17 and 80 under 35 U.S.C. § 112, first paragraph, has been addressed. Applicants respectfully request the withdrawal of the instant rejection, and the allowance of claims 1-17 and 80.

III. Discussion of the New Claim

New claim 81 has been added. Support for the new claim can be found throughout the specification as filed, including particularly at page 12, lines 4-9. Additional support can be found at page 13, lines 11-17, in original claims 42 and 55, in Figure 2, and in the Sequence Listing. Thus, no new matter has been introduced by the addition of new claim 81.

Applicants respectfully submit that claim 81 is believed to comply with 35 U.S.C. § 112, first paragraph, for the reasons set forth hereinabove with respect to the claims in general, and claim 5 in particular. Specifically, applicants respectfully submit that claim 81 recites the method of claim 5, wherein the polymorphism results in a norepinephrine transporter comprising an amino acid sequence as set forth in SEQ ID NO: 4. Applicants respectfully submit that SEQ ID NO: 4 presents the amino acid sequence of a human NET polypeptide with a proline residue at position 457. Applicants respectfully submit that the Patent Office has already conceded that the method is enabled for a polymorphism encoding this amino acid change.

Accordingly, applicants respectfully submit that claim 81 is in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

In light of the above Remarks it is respectfully submitted that the present application is now in proper condition for allowance, and such action is earnestly solicited.

If any minor issues should remain outstanding after the Examiner has had an opportunity to study the Amendment and Remarks, it is respectfully requested that the Examiner telephone the undersigned attorney so that all such matters may be resolved and the application placed in condition for allowance without the necessity for another Action and/or Amendment.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies or credit any overpayments associated with the filing of this correspondence to Deposit Account Number **50-0426**.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

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